Maintenance Cognitive Stimulation Therapy programme for dementia: a single-blind, multi-centre, pragmatic randomised controlled trial.

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ABSTRACT

BACKGROUND:

There is good evidence for the benefits of short-term cognitive stimulation therapy for dementia but little is known about possible long-term effects.

AIMS:

To evaluate the effectiveness of maintenance cognitive stimulation therapy (CST) for people with dementia in a single-blind, pragmatic randomised controlled trial including a substudy with participants taking acetylcholinesterase inhibitors (AChEIs).

METHOD:

The participants were 236 people with dementia from 9 care homes and 9 community services. Prior to randomisation all participants received the 7-week, 14-session CST programme. The intervention group received the weekly maintenance CST group programme for 24 weeks. The control group received usual care. Primary outcomes were cognition and quality of life.

RESULTS:

For the intervention group at the 6-month primary end-point there were significant benefits for self-rated quality of life (Quality of Life in Alzheimer's Disease (QoL-AD) P = 0.03). At 3 months there were improvements for proxy-rated quality of life (QoL-AD P = 0.01, Dementia Quality of Life scale (DEMQOL) P = 0.03) and activities of daily living (P = 0.04). The intervention

subgroup taking AChEIs showed cognitive benefits (on the Mini-Mental State Examination) at 3 (P = 0.03) and 6 months (P = 0.03).

CONCLUSIONS:

Continuing CST improves quality of life; and improves cognition for those taking AChEIs. Further research should evaluate whether long-term CST should be provided more frequently than once a week.

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INTRODUCTION

There is good evidence for the benefits of cognitive stimulation for people with dementia.[1] A recent Cochrane review showed that cognitive stimulation improved both cognition and quality of life.[2] The review concluded the benefits of cognitive stimulation enhanced those of medication, which was effective whether or not acetylcholinesterase inhibitors (ACHEIs) were prescribed.[2] The 2011 World Alzheimer report concluded “there is strong evidence to support cognitive stimulation programmes and these interventions should therefore be routinely offered".[3]

Cognitive Stimulation Therapy (CST) is a well-defined evidence-based version of cognitive stimulation,[4] developed following review of a related approach known as Reality Orientation (RO).[5] We evaluated CST in a pilot trial,[6] followed by a full trial,[4] and developed a manual[7] and a training DVD. CST is now used widely across the UK and in several other countries. A pilot study of maintenance CST which continued for an extra 16 weekly sessions beyond the standard seven-week (14-session) CST programme[8] found a significant improvement in cognitive function compared with CST alone.

The Cochrane Review found no link between duration or frequency of the programme and degree of improvement.[2] Some studies have continued cognitive stimulation for six months or more,[9,10] but there is little evidence about how far potential benefits may continue after sessions end. The Cochrane Review suggested that effects on cognition continue for at most three months;[2] and another study found no continuing effects at ten months.[11]

This trial aimed to evaluate the effectiveness of Maintenance CST in improving cognition and quality of life in people with dementia who have completed standard CST, in comparison with standard CST only followed by usual care after.[12] In addition, a sub-study focused on the effects of maintenance CST on people with dementia taking ACHEIs.

METHODS

Study Design

This was a single-blind, multi-centre, pragmatic randomised controlled trial comparing (1) Maintenance CST groups after completing standard CST vs (2) standard CST only followed by usual care.[13] There was no modification in design or eligibility criteria from the study protocol[12] available at http://www.trialsjournal.com/content/pdf/1745-6215-11-46.pdf.

Participants

Potential centres were screened for eligibility to determine whether there were sufficient numbers of potential participants with dementia, using the inclusion criteria flow chart. Participants met the DSM-IV criteria for dementia;[14] using the diagnostic algorithm and most had either Alzheimer's disease or vascular dementia. All had mild to moderate dementia on the Clinical Dementia Rating scale;[15] could communicate, hear and see well enough to participate in the group; had no major physical illness or disability, or diagnosed learning disability. All trial participants completed seven weeks of CST[4] comprising fourteen twice-weekly 45-minute sessions according to the CST manual.[8] We recruited approximately half of the participants from nine care homes, and half

from nine community services which included Community Mental Health Teams, day centres and voluntary organisations within London, Essex and Bedfordshire. The community centres included four voluntary sector specialist dementia day centres and five centres based in local community mental health teams for older people. The nine care homes included five provided by Social Services, one by the private sector, and three by a voluntary organisation. Of 21 centres approached, one refused and two had too few eligible participants. The study was approved by the Barking & Havering
Local Research Ethics Committee in October 2008 (ethical approval reference number: 08/H0702/68).

Intervention

After completion of the CST programme participants were randomised within each centre to either the (1) intervention group 24-week Maintenance CST programme;[16] or (2) the usual care control group. Usual care varied across the 18 centres but other activities were generally available to both groups.

The Maintenance CST programme was based on the theory of cognitive stimulation as applied to the original CST programme.[4] guided by the MRC framework for complex interventions.[17,18] Each Maintenance CST session has a specific theme or activity (e.g. current affairs; my life; word games) within a consistent structure including orientation-based activity, refreshments and a group song. Each group had two facilitators, one from the research team and one staff member from the participating centre (i.e. care home or community service). All facilitators had at least one year of experience in dementia care, and had attended the one-day CST training course.

Outcome measures

Participants were interviewed at baseline, before randomisation, at three months (intermediate end point) and after six months (primary end point). Researchers collected the proxy ratings of the quality of life measures, the NPI and the ADCS-ADL in structured interviews – with staff for participants in care homes, and with family carers for those in the community.

Primary outcomes

(1) Alzheimer's Disease Assessment Scale – Cognition Subscale (ADAS-Cog). This is the standard cognitive test used in clinical trials for dementia.[19] This comprises 11 tasks measuring memory, language, praxis, attention and other cognitive abilities. Lower scores reflect better cognition.

(1) Quality of Life in Alzheimer's Disease scale (Qol-AD)[20]. This is recommended by the European consensus on outcome measures for psychosocial interventions in dementia.[21] This covers 13 domains of quality of life, and has good internal consistency, validity and reliability. Higher scores reflect better quality of life.

Secondary outcomes

(1) Mini-Mental State Examination (MMSE), a brief but widely used generic test of cognitive function.[22] This is easier to complete than the ADAS-Cog, but still has good reliability and validity.

(2) Dementia Quality of Life scale (DemQoL).[23] The DemQoL covers five domains of quality of life and uses both self reporting and rating by

family carer or staff member as proxy. It has good internal consistency, inter-rater reliability and concurrent validity and can generate a measure of utility.

(3) Neuropsychiatric Inventory (NPI).[24] This assesses 10 behaviours that commonly occur in dementia and has good validity and reliability. Lower scores on this specific measure reflect better behaviour. Total score by frequency x severity of each behaviour

(4) Alzheimer's Disease Co-operative Study-Activities of Daily Living (ADCS-ADL). This validated questionnaire assesses functional capacity over the range of dementia severity.[25] By summing competencies this measure gives high scores to more able respondents.

Sample size

Based on the Cochrane Review we estimated effect size for Maintenance CST of 0.39 on the ADAS-Cog with power of 80% when using 5% significance level and estimating attrition at 15% between baseline and six months. This required a sample size of 230 participants randomised at baseline and an estimated 195 at follow up. With an estimated 60 participants with Alzheimer's disease and taking AChEIs, this provided sufficient numbers for the maintenance CST/AChEIs sub-study to estimate effect size and the feasibility of a full scale trial.

Randomisation

All participants completed the initial CST programme13 and were then allocated at random between (a) the intervention group receiving weekly maintenance CST for 24 weeks (maintenance CST group) or (b) the control group receiving TAU (TAU group). The North Wales Organisation for Randomised Trials in Health (NWORTH) Clinical Trials Unit remotely randomised participants in equal proportions between groups after stratifying for: centre (community service or care home), whether ACHEI was prescribed, and previous CST group (www.bangor.ac.uk/imscar/
nworth/). The random allocation sequence was computer-generated and in the ratio of 1:1. The NWORTH clinical trials unit emailed the individual allocation to the site researcher delivering the intervention and stored the allocation list under a secure password, which was not available to any study site staff. The scheduled treatment sessions, session records and participant records were saved at the site, strictly separated, and distant from the coordinating study centre. Once the trial was completed in each centre, records were transferred to the coordinating study centre and stored by the study centre administrator who was not involved in the assessment process or data analysis. This was in order to avoid contamination. The nature of the intervention prevented us from blinding participants to their allocated group. However blind researchers conducted initial and subsequent interviews, generally in care homes or participants' own homes. The statistician conducting the data analysis was also blind to group assignment.

Statistical analysis

We used the MACRO system to manage the data (version 3.0.84 on Windows 2003 R2; Infermed, London, UK, www.infermed.com). Data was entered manually and audited internally for typing errors by hand, in order to ensure a low error rate. Data was transferred to SPSS version 20 on Windows 7 and audited externally by NWORTH with hard copies of assessments. These audits entailed cross checking a random 10% sample of the electronic data with the paper records to ensure accurate entry. Both random and systematic data entry errors were identified and corrected. As the audits were carried out in parallel with data entry systematic errors could be corrected at an early stage. For participants with some follow-up data, we imputed individual data missing within a scale according to the validated rules for that scale; and missing total scores by multiple regression on variables including allocated group, age, gender, ethnicity, marital status, whether prescribed an ACHEI, staff or family caregiver, centre type and individual centre (using random effects). We adopted a forward stepwise model, and used baseline scores to help predict scores at three months, then both of these to predict scores at six months, since no participant missing at three months returned at six months.

Primary analyses by treatment allocated used analysis of covariance to adjust all imputed data for baseline differences in age, gender, ethnicity, marital status, prescription of ACHEIs, proportion of family caregivers, individual centre (using random effects) and baseline score on the variable under analysis. We then estimated the effect of treatment from the resulting model. The maintenance CST/ ACHEIs trial platform followed the same methodology as for the primary analysis and used the interaction term between ACHEIs and the

treatment group to identify any effect between the two factors for the outcome measures.

Results

The recruitment period took place between January 2009 and September 2010. The final 24-week follow up was completed in May 2011. Of 272 people with dementia that started the CST groups and were considered for the trial, 36 were withdrawn (Table 1). We followed up 218 participants (92% of 236; 96% of those still alive) at 3 months and 199 (84% of 236; 89% of those still alive) at 6 months. The CONSORT flowchart (Figure 1) records the reasons for subsequent withdrawals. Furthermore the withdrawal rate was similar in both arms of the trial.

Of the 236 participants, 123 were allocated to the Maintenance CST group and 113 to usual care. The groups were well matched at baseline and randomisation avoided imbalances (Table 2). The mean age was 83 years and most participants were white females. On average participants allocated to the Maintenance CST groups attended 18 of the 24 available sessions.

Outcomes

At the six-month primary end-point (Table 3), in terms of primary outcomes, the Maintenance CST group had higher scores than controls on self-rated QoL-AD which reached borderline statistical significance with mean difference 1.78 (95% CI 0.00 to 3.60; p=0.05). There were no significant differences on ADAS-Cog, the other primary outcome. There were no significant differences in secondary outcomes at six months. There were two types of centre studied,

care homes and community services. There were significant differences between the centres over and above that explained by centre type.

At three months there were no significant differences on primary outcomes. For secondary outcomes, participants randomised to the intervention group had significantly better scores than controls on proxy ratings of quality of life (QoL-AD and DEMQOL) and daily activities. The mean difference on the proxy QoL-AD was 1.53 (95% CI 0.35 to 2.71; p=0.01); and for the proxy DEMQOL it was 3.24 (95% CI 0.24 to 6.24; p=0.03). The difference on the ADCS-ADL was 2.64 (95% CI 0.04 to 5.24; p=0.04).

Quality of maintenance CST programme provision

To estimate the quality of the maintenance CST provision after each session the researchers made ratings on a range of factors related to the successful running of the groups: manager's attitude (0-2), centre atmosphere (0-2), co facilitators input (0-2), group atmosphere (0-2), and average attendance at sessions (0 = less than 12, 1 = 13–20, 2 = 21-24) with higher scores indicating better quality. Centres were divided into low quality (score 0-5) and high quality (score 6-10). Eight out of 9 community centres scored as high quality compared to only 6 out of 9 care homes. The quality indicator was incorporated into the model of analysis with primary outcome results, with baseline score, centre type, age and allocation as a fixed effect and within a random effect of centre nested within the interaction of quality and type. The analysis showed that both centre type and quality of CST provision were not significant in the model using either

QoL-AD or ADAS-Cog. There were differences among the centres that could not be explained by amount of sessions attended or quality of CST provision.

Maintenance CST/ ACHEI trial platform results

There were no significant results in relation to primary outcomes. Table 4 shows the observed means and SD at baseline. The means and SDs presented at follow-ups 1 and 2 are adjusted for the factors and covariates in the fitted model including the treatment group by ACHEIs interaction term. The follow-up means are standardised to a common baseline mean value. The significance levels quoted are for the interaction term. Only for MMSE at both three and six months follow up were significant results found. The results show that starting from a mean baseline MMSE of 17.8 there was the smallest decrease to 17.25 (95% CI 14.63 to 19.87, p=0.03) at follow up 2 in those taking ACHEIS and receiving maintenance CST. The largest decrease occurred in those taking ACHEIs but with no maintenance CST where the mean was 14.62 (95% CI 11.81 to 17.43, p=0.03). There were no other significant differences between groups in any other outcome measures.

Between baseline and second follow-up, 92% had no changes to their AChEI status with 3 participants stopping (1 in the TAU group and 2 in the maintenance CST group) and 11 starting (4 in the TAU group and 7 in the maintenance CST group) medication. There were no differences between the groups (intervention and control) in the number of reported adverse events or severity. In the intervention group there were five deaths and four withdrawals due to health issues. In the usual care group there were six deaths and five

withdrawals due to health issues. All events were judged as unrelated to trial treatment or assessment contacts by the study trial coordinator and Principal Investigator.

DISCUSSION

Principal findings

Cognitive stimulation for people with dementia is recognised as being effective[2,13] and cost-effective[26], and CST in particular improves both cognition and quality of life.[4,13] This trial finds that after the initial CST programme, a further 24-week course of weekly Maintenance CST improves quality of life at six-months follow-up but confers no additional benefit to cognition. At six months it was only participants who reported improved quality of life (a small standardised difference of 0.35), whereas at three months only the proxy respondents (carers/care staff) noted the improvement (a small standardised difference of 0.30). Participants in the intervention group also improved in their activities of daily living at three months (a very small standardised difference of 0.15). There were no significant differences in other outcomes at either three or six months.

The sub-study results suggest that people on ACHEI medication may benefit cognitively from maintenance CST, suggesting an additive effect which is in line with other studies combining ACHEIs and cognitive stimulation[4,8,13,] and the Cochrane review[2] which found that the effect of cognitive stimulation on cognition is over and above the effects of medication alone. The relevance in terms of clinically significant change is less clear. A mean decrease of 1 point versus 4 points on the MMSE scale may make a big difference for some people

with dementia. The difference might translate into economic benefits since a difference of 1 point in the MMSE score may be associated with substantial reductions in the costs of caring for people with dementia[37]. The CST programme prior to baseline resulted in mean improvements of 4.4 points on the ADAS-Cog and 2.7 points on the MMSE[13]. Since dementia is associated with progressive cognitive decline, there may have been limited potential for further cognitive improvement with the maintenance programme. This means that at six-months follow-up both groups were likely to have declined from the baseline taken after the CST groups finished, and so significant differences in cognition were only likely to be found if the usual care (CST only) group had declined more than the maintenance group.

Strengths and limitations

As participants came from nine care homes and nine community services across London, Essex and Bedfordshire, this pragmatic trial is likely to be generalisable in many respects. However, since participants were almost all white it is hard to say how far CST is useful for other ethnic or cultural groups. Nevertheless, we have recently adapted the CST programme for a south Asian population and successfully run a local group in Hindi and Gujarati. Although we took great care to blind our researchers to allocated treatment, we could not blind those carers who provided proxy ratings for four measures (ADCS-ADL, NPI, QoL-AD and DEMQOL) and this means there is a risk of detection bias. Notably these measures provided three of the four significant findings. Compared to the original CST study this trial had more diversity in dementia severity due to a much higher proportion recruited from the community (50% vs

15%). This resulted in the standard deviations of the cognitive measures being much higher than in the original trial of CST[4]. A larger trial might find significant differences in cognition after weekly Maintenance CST. However, it may be that more frequent groups would be more efficacious.

This was the first rigorous trial of Maintenance CST. The results are inconclusive and suggest that further trials are needed. In particular it would be important for other groups to evaluate Maintenance CST.[38]

Future research could look in more depth at the optimum frequency and duration of CST groups, for example to continue to provide CST twice a week (rather than once weekly) for a 6-month period. Another option would be to repeat the standard 7-week CST programme after a 4-month break. However, this option could be disruptive to the groups, and would not mirror the standard approach used in drug interventions that are given without interruption rather than as a short course. Meaning of the study for clinicians and policymakers

Clinical implications

In the previous stage of this study before and after CST (prior to randomisation) we found that both cognition and quality of life significantly improved, including for those people on AChEIs.[13] However following Maintenance CST at six-month follow-up we found no significant differences in cognition. There were no differences on the ADAS-Cog although the MMSE showed a 0.85 points advantage for the Maintenance CST group. This does not suggest that Maintenance CST has substantial effects on cognition over and above the original benefits of the initial CST programme.[2] Generally, MMSE scores in mild to moderate dementia generally decrease by 2 to 4 points per year,[26]. Before

the initial CST programme[13] (2 months before the start of this RCT) the mean ADAS-Cog was 35.0 and the mean MMSE score was 15.8. Eight months later at six-month follow-up there was no overall cognitive decline with the mean ADAS-Cog scores being 35.9 and 35.3 and the mean MMSE scores being 16.3 and 15.5 in the treatment and control groups respectively. From a standardised baseline score of 17.75 on the MMSE; in the ACHEI only group, MMSE scores fell to 14.60 points in the 6 months of the maintenance CST trial; compared with a decrease to 17.25 in the maintenance CST/ACHEI (combined) treatment; and a decrease of 16.26 in the maintenance CST only group. This suggests that CST may continue to have some degree of protective effect on cognition over and above the effects of medication. Other studies using usual care control groups have also found that a programme of cognitive stimulation sessions over a longer time period can be effective in reducing cognitive decline in dementia.[27,28]

In chronic conditions quality of life may be more important for older adults than disease-specific outcomes and it is a key outcome that interventions for dementia should target. Benefits to cognition alone may not be sufficient to justify an extensive programme of intervention unless they are accompanied by other benefits such as quality of life improvements[29]. Two recent systematic reviews highlighted that there are few well-designed studies on the effectiveness of either pharmacological[33] or psychosocial[34] interventions on quality of life. Like other follow up studies we found that individual changes in quality of life were apparent for nearly three-quarters of our sample[30,31,32]. In contrast to the Cochrane review of cognitive stimulation our study found that activities of daily living improved at three-month follow-up. However, previous

research[35] suggests that there may be a correlation between proxy rated quality of life and activities of daily living. It might be that the effects of the intervention on proxy rated quality of life was linked with the effects on activities of daily living. At six month follow up these proxy rated domains showed no difference. However, for the person with dementia a temporary improvement in quality of life, cognition, or activities of daily living may all be considered worthwhile

Future research

As this was the first rigorous trial of Maintenance CST, we encourage others to implement and evaluate this novel extension in other populations in other contexts with other staff. In our research programme we have three further CS studies[37] Firstly, we are undertaking a pragmatic cluster randomised implementation trial to compare staff trained in CST receiving either (1) additional support (web support, regular phone support) or (2) no support. This will evaluate whether additional staff support results in more CST group attendances. Secondly, we are conducting an implementation in practice study measuring minimal outcomes (cognition and quality of life) for centres running CST/Maintenance CST groups. Lastly, we have developed a version of CST for use by the family carer (individual CST) and this is currently being evaluated in a large multicentre trial funded by the National Institute of Health Research/Health Technology Assessment programme.

CONCLUSIONS

Standard CST can improve cognition and quality of life. This trial indicates that weekly Maintenance CST over 24 weeks adds little beyond the basic CST

programme. Nevertheless, over the 8 months (from the original baseline before 2 months of CST and the six-month follow-up), the average cognitive decline in both the maintenance CST and usual care groups was considerably less than would normally be expected in practice suggesting the original CST programme had some residual beneficial effect. Further research should evaluate whether long-term CST should be provided more frequently than once a week. Over the 8 months (from the original baseline before 2 months of CST and the 6-month follow-up), the average cognitive decline in both the maintenance CST and TAU groups was considerably less than would normally be expected in practice suggesting the original CST programme had some residual beneficial effect. Maintenance CST may offer short and long term benefits to quality of life. The sub study of maintenance CST with ACHEIs provides initial evidence that maintenance cognitive stimulation therapy in combination with ACHEI medication may have longer term benefits to cognition. Pharmacological and psychosocial interventions may potentially work better together than either alone.

What this paper adds

What is already known on this subject

- The Cochrane Review of cognitive stimulation found that it can improve cognition and quality of life for people with dementia.
- There is only limited evidence about the effects of longer term cognitive stimulations programmes
- Little is known about how long or how often to continue cognitive stimulation sessions beyond a short term programme

What this study adds

- This trial suggests that maintenance cognitive stimulation may improve quality of life, but not cognition over six months
- There is initial evidence to suggest that maintenance cognitive stimulation therapy in combination with ACHEI medication may have longer term benefits to cognition
- Cognitive decline was less than expected for both the CST only (usual care) and CST/maintenance CST (intervention) groups

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Contributors

All 10 authors participated and contributed to design and conduct of the SHIELD-Maintenance CST trial, commented on drafts, and approved the

version to be published. MO led the study. EA and ASt recruited the participants, run the assessments and interventions. EA, ZH and CW analysed the data and, with MO, ASt, JH, IR and BW interpreted the data. All authors approved the final manuscript. MO is the guarantor.

More specifically:

Martin Orrell was principal applicant and chief investigator; he led the design and execution the trial, and the writing of this paper

Elisa Aguirre implemented the design and overall organisation of the trial; managed the development of the programme; recruited all centres that took part in the trial; recruited and assessed participants; ran some of the intervention groups and produced the initial draft of the paper.

Aimee Spector was a co-applicant and provided clinical supervision for the researchers running the intervention.

Zoe Hoare was trial statistician; she led data management and analysis.

Robert Woods was co-applicant and principal investigator for clinical psychology.

Amy Streater recruited and assessed participants; run some of the intervention groups, entered data and run some audits of the trial.

Helen Donovan was Bedfordshire site coordinator.

Juanita Hoe was the SHIELD clinical trial coordinator, coordinated the programme and assessed the adverse events.

Ian Russell was co-applicant and trial methodologist.

Christopher Whitaker undertook validatory statistical analysis, and contributed to interpreting data.

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Competing interest

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval

The study was approved by the Barking & Havering Local Research Ethics Committee, ethical approval reference number: 08/H0702/68 in October 2008.

Data sharing

The dataset is available from the corresponding author at m.orrell@ucl.ac.uk. Participants' consent was obtained, but the data presented are anonymised and risk of identification is low.

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Figure 1. Consort flowchart of participants' progress

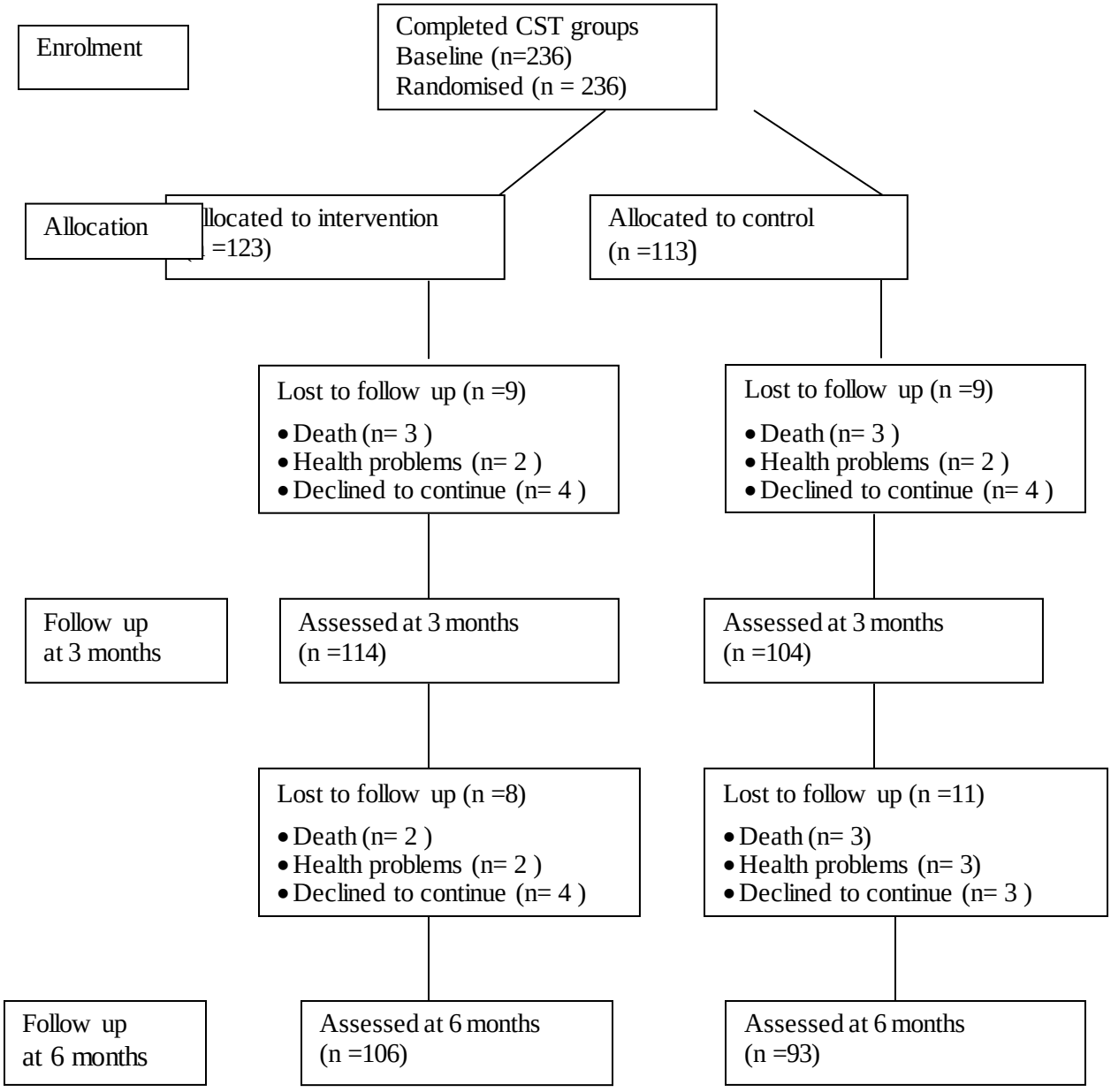

Table 1. Baseline characteristics of 236 participants in maintenance CST trial

Participants at Baseline 0 - Before start of CST groups	272
Total lost from the beginning of CST groups	36
Reason for withdrawal	
Did not like CST groups and wanted to withdraw	17 (49%)
Health issues	15 (40%)
Difficulties with group time or other participants	2 (6%)
Moved to a different care home	2 (6%)
Participants at Baseline 1 - After completion of CST groups	236

Table 2. Baseline characteristics of 236 participants by allocated group

Characteristics	Intervention (n=123) Number (%)	Control (n=113) Number (%)
Female	80 (65%)	70 (62%)
Ethnicity: white	111 (90%)	104 (92%)
Marital status (widow)	54 (44%)	57 (50%)
Dementia diagnosis (AD)	38 (31%)	35 (31%)
On AChEIs	42 (34%)	34 (30%)
In Care Home	51 (41%)	50 (44%)
	Mean (SD)	Mean (SD)
Age (years):	82.7 (7.9)	83.5 (7.2)
ADAS-Cog score	31.1 (14.6)	33.2 (13.0)
QoL-AD score	36.1 (4.8)	36.5 (5.7)
MMSE score	17.8 (5.6)	17.8 (5.4)
DEMQOL score	94.8 (10.9)	95.1 (11.7)
NPI score	13.8 (12.9)	11.3 (9.1)
ADCS-ADL score	42.7 (17.2)	41.5 (18.1)
Proxy QoL-AD score	33.7 (5.9)	33.3 (4.9)
Proxy DEMQOL score	102.2 (13.5)	102.2 (11.2)

Table 3. Effects of Maintenance CST on adjusted imputed outcomes at primary and secondary end points

	Primary end point - 6 month follow up				Secondary end point 3-month follow up			
Adjusted outcomes	Treatment Mean (SE)	Control Mean (SE)	Difference[a] Mean (SE)	Significance level	Treatment Mean (SE)	Control Mean (SE)	Difference[a] Mean (SE)	Significance level
ADAS-Cog[b]	35.94 (2.79)	35.29 (2.85)	-0.65 (1.55)	.68	35.32 (2.56)	34.47 (2.59)	-0.85 (1.29)	.51
QoL-AD[c]	35.62 (1.43)	33.84 (1.53)	1.78 (0.91)	.05	34.29 (1.03)	33.97 (1.04)	0.32 (0.61)	.60
MMSE[c]	16.34 (1.21)	15.49 (1.25)	0.85 (0.58)	.15	16.09 (0.88)	15.79 (0.91)	0.30 (0.52)	.57
DEMQOL[c]	89.13 (3.55)	88.83 (3.56)	0.30 (1.52)	.84	89.85 (2.34)	90.71 (2.38)	-0.86 (1.31)	.51
NPI[b]	18.76 (3.78)	20.35 (3.94)	1.58 (2.16)	.47	14.71 (2.84)	16.18 (2.76)	1.47 (1.55)	.34
ADCS-ADL[c]	43.29 (2.88)	42.35 (2.87)	0.94 (1.51)	.53	43.58 (2.32)	40.94 (2.32)	2.64 (1.30)	.04
Proxy QoL-AD[c]	34.12 (1.41)	34.05 (1.41)	0.07 (0.74)	.93	33.93 (1.05)	32.40 (1.07)	1.53 (0.59)	.01
Proxy DEMQOL[c]	97.75 (3.23)	96.61 (3.21)	1.13 (1.71)	.51	101.36 (2.67)	98.12 (2.67)	3.24 (1.50)	.03

a Positive differences favour maintenance CST.

b Lower scores show better outcome

c Higher scores show better outcome

Table 4. Effects of Maintenance CST on adjusted imputed outcomes at primary and secondary end point according to ACHEI treatment. The significance levels quoted are for the interaction term of treatment group and receipt of AChEIs.

		Baseline		3 months			6 months		
Group	n	Mean	SE	Model adjusted mean	SE	Interaction p	Model adjusted mean	SE	Interaction p
ADAS-Cog						.13			.71
ACHEI	34	31.29	2.09	37.05	2.84		36.52	3.53	
TAU	79	34.03	1.5	32.35	2.68		34.67	2.97	
ACHEI/MCST	42	28.65	1.78	36.55	3.16		35.77	3.28	
MCST	81	32.4	1.77	33.85	2.57		35.99	2.98	
QOL-AD						.97			.48
ACHEI	34	37.73	.76	32.81	1.23		33.94	1.86	
TAU	79	35.99	.69	35.13	1.09		33.81	1.52	
ACHEI/MCST	42	37.08	.77	33.14	1.27		34.72	1.7	
MCST	81	35.62	.53	35.45	1.05		36.07	1.44	
NPI						.99			.26
ACHEI	34	12.13	1.62	17.23	3.28		23.78	4.54	
TAU	79	11	1.01	15.12	2.86		17.15	4.11	
MCST/ACHEI	42	16.15	2.73	15.85	3.39		18.21	4.47	
MCST	81	12.65	1.05	13.61	2.82		17.49	3.79	
ADL						.80			.80
ACHEI	34	44.03	2.88	41.51	2.79		42.45	3.34	
TAU	79	40.42	2.10	40.37	2.47		42.22	3.04	
MCST/ACHEI	42	48.24	2.87	43.83	2.87		43.91	3.46	
MCST only	81	39.78	1.75	43.17	2.34		42.91	2.92	
MMSE						.03			.03
ACHEI	34	18.85	.79	15.26	1.08		14.62	1.40	
TAU	79	17.33	.63	16.25	.92		16.26	1.28	
MCST/ACHEI	42	18.27	.84	17.17	1.06		17.25	1.33	

MCST	81	17.55	.64	15.77	.88	16.26	1.26
DEMQOL					.92		.97
ACHEI	34	97.90	1.51	89.13	2.81	87.93	3.90
TAU	79	93.86	1.42	92.25	2.51	89.75	3.74
ACHEI/MCST	42	97.36	1.53	88.99	2.89	87.88	3.86
MCST	81	93.49	1.26	91.04	2.37	90.22	3.69